State of the ART: The New DHHS HIV Treatment Guidelines and Current Controversies in Antiretroviral Therapy

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Since their original publication on April 24, 1998, the Department of Health and Human Services' *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents* have undergone significant alterations. Research into the optimal times to start and switch therapy, along with the evaluation of both new and older antiretroviral regimens and laboratory assays, has evolved considerably over the past five years—a reflection of scientific discovery that continues to change the standard of care for HIV-infected individuals.

Dr. Mark Dybul, Co-Executive Secretary of the Panel on Clinical Practices for Treatment of HIV Infection responsible for the *Guidelines*—and no stranger to the pages of *The PRN Notebook*—helped to kick off PRN's 12th year of service to discuss changes made to the *Guidelines* that reflect the advances (and setbacks) made in recent years. Dr. Dybul's presentation focused on a version of the *Guidelines* released on July 12, 2003, which reflected a number of significant changes made to the February 4, 2002 *Guidelines*. However, true to its self-categorization as a "living document," the *Guidelines* have been updated yet again—after Dr. Dybul's September lecture—and were officially released on November 10, 2003. In turn, this article has been rewritten to reflect the most recent published version of the *Guidelines*, while at the same time leaving many of the still-applicable comments by Dr. Dybul intact.

While there is no denying the value of the *Guidelines*, experts acknowledge that no single document can possibly address all of the controversies surrounding antiretroviral therapy. The *Guidelines* themselves point out that controversies exist, including some within the most basic recommendations such as the right time to begin or switch antiretroviral therapy and the particular treatments that should be used by patients under various circumstances. And as clinical research evolves and attempts to answer lingering questions, new controversies may arise and long-standing controversies may deepen considerably.

Building upon Dr. Dybul's overview, Dr. Roy "Trip" Gulick paid a return visit to PRN in October to discuss some of the more notable controversies facing HIV-treating clinicians today. The article combines highlights from both Dr. Dybul's and Dr. Gulick's presentations, including some of the more significant changes that have been made to the *Guidelines*, along with some of the controversies that are discussed—and not discussed—within the *Guidelines*.

I. Initiating Antiretroviral Therapy

A handful of clinical trials, most notably the phase III clinical endpoint studies of the earliest protease inhibitors, have provided strong evidence in favor of treating all HIV-infected patients with CD4+ counts below 200 cells/mm^3. However, it is not recommended that patients wait until their CD4+ counts are below 200 cells/mm^3 to initiate therapy. But herein lies a dilemma: The optimal time to initiate antiretroviral therapy among asymptomatic patients with CD4+ counts greater than 200 cells/mm^3 is not well understood, given the lack of data from studies evaluating clinical endpoints (e.g., progression to AIDS or death) in patients with less advanced HIV disease beginning therapy for the first time. Previous versions of the *Guidelines* recommended antiretroviral therapy for all patients with CD4+ counts below 500 cells/mm^3 and viral loads above 55,000 copies/mL (by PCR). However, there were growing concerns surrounding the possible toxicities, dosing complexities, and risk of resistance associated with available antiretroviral drug regimens. These concerns gave rise to serious debate surrounding the potential risks versus the perceived benefits of initiating antiretroviral therapy early in the course of HIV infection.

More tailored approaches to initiating antiretroviral treatment have since been adopted by the panelists, which was duly noted in the two most recent versions of the *Guidelines*. While viral load remains a factor in deciding when to initiate therapy, it is the CD4+ cell count that carries the greatest weight in making this decision.

While not discussed in the *Guidelines*, Dr. Gulick made reference to a study reported in a 2002 issue of *The Lancet* by Dr. Matthias Egger and an international team of collaborators (Egger, 2002). The study, which involved an analysis of 12,574 HIV-positive patients participating in 13 cohorts in Europe, Canada, and the United States, analyzed various factors contributing to favorable prognoses among individuals initiating antiretroviral therapy for the first time. During 24,310 person-years of follow up, 1,094 patients either developed AIDS or died. The baseline (pretreatment) CD4+ cell count was strongly associated with the probability of progression to AIDS or death. Compared with patients starting antiretroviral therapy with less than 50 CD4+ cells/mm^3, adjusted hazard ratios for clinical progression/death were 0.74 for 50–99 cells/mm^3, 0.52 for 100-199 cells/mm^3, 0.24 for 200–349 cells/mm^3, and 0.18 for 350 or more CD4+ cells/mm^3. Baseline viral load was associated with a higher probability of progression, only if it was 100,000 copies/mL or higher. Other independent predictors of poorer outcome were advanced age, infection through injection-drug use, and a previous diagnosis of AIDS.

Table 1. **Indications for Initiating Antiretroviral Therapy for the Chronically HIV-Infected Patient**

Clinical Category	CD4+ T Cell Count	Plasma HIV RNA	Recommendation
Symptomatic (AIDS or severe symptoms)	Any value	Any value	Treat
Asymptomatic, AIDS	CD4+ T cells < 200/mm³	Any value	Treat
Asymptomatic	CD4+ T cells > 200/mm³ but < 350/mm³	Any value	Treatment should be offered, although controversial.
Asymptomatic	CD4+ T cells > 350/mm³	> 55,000 (by RT-PCR or bDNA)*	Some experienced clinicians recommend initiating therapy, recognizing that the 3-year risk for untreated patients to develop AIDS is > 30%; in the absence of increased levels of Plasma HIV RNA, other clinicians recommend deferring therapy and monitoring the CD4+ T cell count and level of Plasma HIV RNA more frequently; clinical outcome data after initiating therapy are lacking.
Asymptomatic	CD4+ T cells > 350/mm³	< 55,000 (by RT-PCR or bDNA)*	Many experienced clinicians recommend deferring therapy and monitoring the CD4+ T cell count, recognizing that the 3-year risk for untreated patients to experience AIDS is < 15%.

* Although a 2-2.5 fold difference existed between RT-PCR and the first bDNA assay (version 2.0), with the 3.0 version bDNA assay, values obtained by bDNA and RT-PCR are similar except at the lower end of the linear range (< 1,500 copies/mL).

Source: Panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services (DHHS) and the Henry J. Kaiser Family Foundation. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* [Table 6]. November 10, 2003. Access at: http://www.aidsinfo.nih.gov/guidelines/adult/AA_111003.html#table6

The *Guidelines* now list a CD4+ count below 350 cells/mm³ as the most significant threshold to consider in deciding when antiretroviral treatment is recommended, or should at least be offered to the patient. As discussed in Table 6 of the *Guidelines* (Table 1 in this review), all HIV-positive individuals who are symptomatic or are asymptomatic and have a CD4+ count below 200 cells/mm³—irrespective of the viral load—should be receiving antiretroviral treatment. For patients with a CD4+ count above 200 cells/mm³, but below 350 cells/mm³, most panelists agreed that treatment should be offered, irrespective of the viral load, although this is still considered to be a controversial recommendation. The controversy hinges on a recent evaluation of data from the Multicenter AIDS Cohort Study (MACS) evaluating 231 untreated HIV-positive patients with CD4+ counts between 200 and 350 cells/mm³ (Phair, 2002). Of the 40 (17%) patients with viral loads below 10,000 copies/mL, none progressed to AIDS during three years of follow up. Of 28 (29%) patients with viral loads between 10,000 and 20,000 copies/mL, 11% progressed to AIDS within three years.

For patients with CD4+ counts above 350 cells/mm³ and a viral load above 55,000 copies/mL (either by PCR or bDNA), some panelists recommend initiating therapy. This recommendation is based on data from the MACS, suggesting that the three-year risk for untreated patients to develop AIDS is greater than 30%. Also of interest are recent data from the Swiss HIV Cohort Study, which evaluated the efficacy of early initiation of antiretroviral treatment (Opravil, 2002). In this case-control study, a cohort of 358 asymptomatic patients who initiated antiretroviral therapy between January 1, 1996, and December 31, 1999, with a CD4+ count above 350 cells/mm³ were compared with a cohort of 358 asymptomatic participants who were seen at around the same time and who remained untreated during the following 12 months. Within one to two years of follow-up, 1% of the patients who initiated early antiretroviral therapy had progressed to AIDS, compared to 5% of the patients who delayed therapy (p=0.0001). Mortality rates, irrespective of the cause of death, were also significantly lower in the early-treatment cohort—approximately 1% versus 5% in the delayed-treatment cohort. In multivariable Cox regression analysis, treatment reduced the risk of clinical progression by a factor of fourfold to fivefold. During follow-up, the treated group had significantly higher CD4+ counts and lower HIV-RNA levels. However, it is also important to recognize that 35% of patients who initiated therapy early either changed at least one drug—or stopped therapy—because of intolerance or adverse events. Approximately 41% of patients interrupted therapy at least once for various reasons and 24% remained off treatment at the end of the follow-up period. It's also important to note that this case-control study was not a randomized study of antiretroviral therapy; there may have been bias introduced when selecting which patients to treat.

In the absence of increased viral loads, some panelists recommend deferring therapy, at the expense of monitoring CD4+ cell counts and viral loads more frequently. As for patients with CD4+ counts above 350 cells/mm³ and viral loads below 55,000 copies/mL, most panelists recommend deferring therapy and monitoring the CD4+ cell count and viral load, recognizing that the three-year risk for untreated patients to experience AIDS is less than 15%.

In summary, the "when to start?" question facing asymptomatic HIV-positive patients with CD4+ counts greater than 200 cells/mm³ is complex and must be made in the setting of careful counseling and education. As explained in the *Guidelines*—and reiterated by both Drs. Dybul and Gulick—factors that must be considered in this decision are:

1) the willingness, ability, and readiness of the person to begin therapy;
2) the degree of existing immunodeficiency as determined by the CD4+ cell count;
3) the risk of disease progression as determined by the CD4+ cell count and viral load (as reviewed above);
4) the potential benefits and risks of initiating therapy for asymptomatic persons, including short- and long-term adverse drug effects; and
5) the likelihood, after counseling and education, of adherence to the prescribed treatment regimen.

II. Recommended Antiretrovirals for Initial Therapy

SINCE THE INTRODUCTION OF PROTEASE INHIBITORS AND POTENT COMbination antiretroviral therapy in 1995, a substantial—though well acknowledged as incomplete—body of clinical data has been amassed that helps the selection of initial therapy for the previously untreated patient. There are now 19 unique approved antiretroviral agents—not including the two formulations of didanosine (Videx; Videx EC), stavudine (Zerit; Zerit XR), saquinavir (Invirase; Fortovase), and amprenavir (Agnerase; Lexiva), or the fixed-dose combinations of zidovudine/lamivudine (Combivir) and zidovudine/lamivudine/abacavir (Trizivir)—with which to design regimens of three or more agents. Accordingly, the key table that lists the recommended antiretroviral regimens for antiretroviral-naive patients (Table 12a in the *Guidelines*; Table 2 in this review) has been reformatted "to provide clinicians with a selection of potential antiretroviral combination regimens for initiation of therapy."

"There are a number of factors to consider when choosing a first antiretroviral regimen," explained Dr. Gulick. "Antiretroviral activity, including effects on viral load, CD4+ cell counts, and clinical progression, is certainly at the top of the list of factors. But there are other factors to consider, including durability of responses; tolerability issues, including acute and chronic side effects; and convenience, including the number of pills, dosing intervals, and food requirements. Even with the large number of drugs available, it is still important to choose a first regimen with the intent of preserving future options. There are also patient factors to consider, including the stage of HIV disease, concomitant illnesses, and other medications being used. Finally, and this is something we're really coming to deal with more in recent years, there is access and cost."

The most recent list of recommended antiretroviral drug combinations for initial therapy is noticeably more directive than previous versions of the *Guidelines*. In the February 2002 *Guidelines*, clinicians could draw upon a list of several "strongly recommended" protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs) to be paired with several "strongly recommended" dual-nucleoside reverse transcriptase inhibitor (NRTI) regimens. The most recent version of the *Guidelines* lists only one "preferred" PI and one "preferred" NNRTI, to be combined with one of a select number of lamivudine (Epivir)-based NRTI dual combinations. This choice results from head-to-head comparative studies, demonstration of durable antiretroviral responses, and assessments of comparative toxicities and convenience.

Why Not Nevirapine as a Preferred NNRTI?

EFAVIRENZ (SUSTIVA) IS LISTED AS THE PREFERRED NNRTI OPTION, TO BE combined with lamivudine and either zidovudine (Retrovir), tenofovir (Viread), or stavudine. There have been some lingering questions among clinicians, community advocates, and other experts as to why nevirapine (Viramune) did not also receive "preferred" status, in light of its more recent showing in clinical trials, most notably the 2NN study.

Two early studies comparing nevirapine to PI-based regimens were the Atlantic and Combine clinical trials. Unfortunately, neither trial was adequately powered to establish equivalence of the PI- and nevirapine-based regimens. In the Atlantic study, patients were randomized to receive either indinavir (Crixivan) or nevirapine in combination with didanosine and stavudine. At 96 weeks, 44% of patients in the indinavir arm and 55% of patients in the nevirapine arm maintained viral loads below 50 copies/mL (van Leeuwen, 2003). In the Combine study, nevirapine was compared to nelfinavir (Viracept) in combination with zidovudine and lamivudine. After 12 months, 75% of nevirapine-treated patients and 60% of patients in the nelfinavir arm had a viral load < 200 copies/mL, with no statistically significant difference between the two groups (Podzamczer, 2002). While these are two of the larger studies comparing nevirapine-based regimens to PI-based regimens, fewer than 200 patients received either nevirapine or a PI in these two studies combined.

To get a better sense of nevirapine's efficacy compared to efavirenz, the 2NN study was conducted to compare these two NNRTIs in a large population of antiretroviral-naive patients (van Leeuwen, 2002). As reported at the 6th International Congress on Drug Therapy in HIV Infection, held in November 2002 in Glasgow, 220 patients were randomized to receive 400 mg QD nevirapine, 387 patients were randomized to receive (standard-dose) 200 mg BID nevirapine, 400 patients were randomized to receive 600 mg QD efavirenz, and 209 patients were randomized to receive 400 mg QD nevirapine plus 800 mg QD efavirenz. All patients received standard doses of stavudine and lamivudine in addition to their selected NNRTI.

Treatment failure at 48 weeks was defined as less than 1 log decline in the first 12 weeks, virologic failure from week 24 onward (two consecutive viral load measurements greater than 50 copies/mL), a switch from the assigned treatment drugs, or progression to AIDS or death. Secondary outcomes included the percentage of patients with viral loads below 50 copies/mL after 48 weeks of treatment, changes in the CD4+ cell count, changes in lipid levels, and adverse events.

After 48 weeks of treatment, 43.7% of patients in the BID nevirapine arm and 37.8% of those in the efavirenz arm experienced treatment failure, with no statistically significant difference between the two groups. Similarly, there was no statistically significant difference in the percentage of patients with HIV-RNA levels below 50 copies/mL between these two groups (65.4% in the BID nevirapine arm and 70.0% in the efavirenz arm). What's more, the CD4+ count increase was the same in both groups (160 cells/mm^3).

While these data certainly suggest comparability—or even equivalency—between nevirapine and efavirenz for patients initiating an NNRTI for the first time, the *Guidelines* point out that a 10% difference in treatment failure at 48 weeks between the two treatment groups was prespecified to be a clinically meaningful difference and that the primary objective of the study was to demonstrate noninferiority of the two regimens within this difference. The results of 2NN indicated that a difference of this magnitude cannot be ruled out—based on the upper bound of the 95% confidence interval reported, the advantage of efavirenz over nevirapine at 48 weeks may exceed 10% for major efficacy outcomes.

Another noteworthy difference is the percentage of patients who discontinued treatment because of an adverse event: 21.2% of patients in the BID nevirapine group and 15.5% of patients in the efavirenz group (p=0.04). More patients receiving BID nevirapine than those receiving efavirenz experienced a grade 3/4 clinical hepatotoxicity (2.1% versus 0.3%) and a grade 3/4 laboratory hepatobiliary toxicity (7.8% versus 4.5%). Moreover, two deaths—associated with toxic hepatitis and Steven's-Johnson syndrome—were reported in the BID nevirapine group.

On the basis of the completed 2NN study, along with other relevant data, the *Guidelines* continue to recommend efavirenz over nevirapine as the preferred NNRTI in antiretroviral-naive patients. An exception to this recommendation is the use of NNRTI therapy in pregnant women or women "at risk for" pregnancy. Under these circumstances, preference should be given to nevirapine, as efavirenz has been associated with significant teratogenic effects in nonhuman primates.

Table 2. **Antiretroviral Regimens Recommended for Treatment of HIV Infection in Antiretroviral-Naive Patients**

NNRTI-Based Regimens		Number of pills per day
Preferred Regimens	**efavirenz + lamivudine + (zidovudine or tenofovir DF or stavudine*) — except for pregnant women or women with pregnancy potential****	**3–5 pills**
Alternative Regimens	efavirenz + emtricitabine + (zidovudine or tenofovir DF or stavudine*) — except for pregnant women or women with pregnancy potential**	3–4 pills
	efavirenz + (lamivudine or emtricitabine) + didanosine — except for pregnant women or women with pregnancy potential**	3–5 pills
	nevirapine + (lamivudine or emtricitabine) + (zidovudine or stavudine* or didanosine)	4–6 pills
PI-Based Regimens		**Number of pills per day**
Preferred Regimens	**Kaletra® (lopinavir+ ritonavir) + lamivudine + (zidovudine or stavudine*)**	
Alternative Regimens	amprenavir + ritonavir† + (lamivudine or emtricitabine) + (zidovudine or stavudine*)	12–14 pills
	atazanavir + (lamivudine or emtricitabine) + (zidovudine or stavudine*)	4–5 pills
	indinavir + (lamivudine or emtricitabine) + (zidovudine or stavudine*)	8–10 pills
	indinavir + ritonavir† + (lamivudine or emtricitabine) + (zidovudine or stavudine*)	8–11 pills
	lopinavir/ritonavir (coformulated as Kaletra) + emtricitabine + (zidovudine or stavudine*)	8–9 pills
	nelfinavir§ + (lamivudine or emtricitabine) + (zidovudine or stavudine*)	6–14 pills
	saquinavir (sgc or hgc)Ø+ ritonavirØ + (lamivudine or emtricitabine) + (zidovudine or stavudine*)	14–16 pills
Triple NRTI Regimen – Only as alternative to NNRTI- or PI-based regimen	**Only when an NNRTI- or a PI-based regimen cannot or should not be used as first-line therapy**	**Number of pills per day**
	abacavir + lamivudine + zidovudine (or stavudine*)	2–6 pills

* Higher incidence of lipoatrophy, hyperlipidemia, and mitochondrial toxicities reported with stavudine than with other NRTIs.

** Women with child bearing potential implies women who want to conceive or those who are not using effective contraception.

† Low-dose (100–400 mg) ritonavir

§ Nelfinavir available in 250 mg or 625 mg tablet

Ø sgc = soft gel capsule; hgc = hard gel capsule

This table is a guide to treatment regimens for patients who have no previous experience with HIV therapy. Regimens should be individualized based on the advantages and disadvantages of each combination such as pill burden, dosing frequency, toxicities, and drug-drug interactions, and patient variables, such as pregnancy, comorbid conditions, and level of plasma HIV-RNA. Clinicians should refer to Table 12b (not included in this review) to review the pros and cons of different components of a regimen and to Tables 14–17 (not included in this review) for adverse effects and dosages of individual antiretroviral agents. Preferred regimens are in bold type; regimens are designated as "preferred" for use in treatment naive patients when clinical trial data suggests optimal and durable efficacy with acceptable tolerability and ease of use. Alternative regimens are those where clinical trial data show efficacy, but it is considered alternative due to disadvantages compared to the preferred agent, in terms of antiviral activity, demonstrated durable effect, tolerability or ease of use. In some cases, based on individual patient characteristics, a regimen listed as an alternative regimen in the table may actually be the preferred regimen for a selected patient. Clinicians initiating antiretroviral regimens in the HIV-1-infected pregnant patient should refer to "Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States," at **http://www.aidsinfo.nih.gov/guidelines/**.

Source: Panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services (DHHS) and the Henry J. Kaiser Family Foundation. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* [Table 12a]. November 10, 2003. Access at: http://www.aidsinfo.nih.gov/guidelines/adult/AA_111003.html#table12a

Why is Stavudine Listed as a Preferred NRTI?

STAVUDINE IS PROMINENTLY FEATURED AS AN NRTI OPTION AMONG THE two preferred antiretroviral regimens and many of the alternative antiretroviral regimens. However, there has been some concern among clinicians and community advocacy groups that stavudine is a less than ideal first-line option, given its association with lipoatrophy and other side effects.

Both the July and November 2003 versions of the *Guidelines* were amended to reflect these concerns. In Table 12a of the *Guidelines* (see Table 2 in this review), lamivudine paired with either zidovudine or stavudine are listed throughout as preferred NRTI regimens. However, in the text explanation of this recommendation, the *Guidelines* clearly state that, "the Panel recommends a combination of lamivudine with zidovudine as the two-NRTI combination of choice as part of a combina-

tion regimen. Combination of lamivudine with stavudine or tenofovir may be used as alternative." And while the DHHS Panel agreed that the combination of stavudine with lamivudine is widely used, the *Guidelines* clearly state—both in the text discussing the selection of preferred regimens and Table 12a—that stavudine may be more frequently associated with dyslipidemia, lipoatrophy, and mitochondrial toxicities. What's more, the November 2003 version of the *Guidelines* now specifies that regimens containing both stavudine and didanosine are not recommended given the high incidence of toxicities and reports of serious lactic acidosis. The only time these two drugs should be coadministered is when no other antiretroviral options are available and the potential benefits outweigh the risks.

So why does stavudine appear as a preferred NRTI in the table of recommended drug combinations? "Stavudine is widely prescribed, is well studied, and has been shown to be efficacious," Dr. Dybul commented. "Many of the adverse events that are of greatest concerns have been seen when stavudine is combined with didanosine, which is not a preferred NRTI combination. Finally, clinicians and patients need options."

Why are Triple NRTI Regimens Listed at All?

ABACAVIR (ZIAGEN), COMBINED WITH LAMIVUDINE/ZIDOVUDINE OR lamivudine/stavudine, is listed as an alternative to PI- and NNRTI-based regimens in Table 12a of the *Guidelines*. This has also been a source of confusion, given the conflicting results from clinical trials evaluating abacavir-based regimens.

The first noteworthy clinical trial was CNAAB 3005, which was conducted to determine if a regimen containing abacavir and zidovudine/lamivudine (Combivir) was comparable to one containing indinavir and Combivir in terms of reducing viral load to less than 400 copies/mL after 48 weeks of treatment (Staszewski, 2001). In the intent-to-treat analysis, 51% of patients in both groups had undetectable viral loads after 48 weeks. However, in patients with baseline viral loads in excess of 100,000 copies/mL, the proportion achieving less than 50 copies/mL was greater in the indinavir group than in the abacavir group (45% vs. 31%, respectively).

Important data also comes from ACTG study A5095, a randomized, double-blind, placebo-controlled Phase III trial that compared three PI sparing regimens in antiretroviral naive patients: abacavir/zidovudine/lamivudine versus efavirenz/zidovudine/lamivudine versus efavirenz/abacavir/zidovudine/lamivudine (Gulick, 2003). After an average of 32 weeks of therapy, the unblinded results showed a higher incidence of, and earlier time to, virologic failure—defined as a viral load above 200 copies/mL at least four months after starting treatment—in the triple-NRTI arm compared to the pooled efavirenz-based arms ($p<0.001$). This difference was evident regardless of whether the baseline HIV-RNA levels were greater than or less than 100,000 copies/mL. These results led to the premature closure of the triple-NRTI arm of the study.

"Based on the results of these studies," Dr. Dybul explained, "the panel did not feel that abacavir combined with lamivudine and either zidovudine or stavudine should be listed as a preferred regimen. However, the panel does feel that these regimens may be used as an alternative regimen where other options may be less desirable due to concerns over toxicities, drug interactions, or regimen complexity." In turn, abacavir with either zidovudine/lamuvidine or stavudine/lamivudine is listed as an alternative regimen, only when an NNRTI- or a PI-based regimen cannot or should not be used as first-line therapy.

Two triple-NRTI regimens that clearly should not be used consist of tenofovir/lamivudine/abacavir and tenofovir/lamivudine/didanosine EC.

The recommendation not to use tenofovir/lamivudine/abacavir—at least not without either a protease inhibitor or NNRTI—is based on data demonstrating a high rate of early virologic non-response in a GlaxoSmithKline-sponsored clinical trial (ESS30009) of treatment-naive HIV-positive individuals receiving these three drugs, all once daily (Gallant, 2003).

This study was a randomized, open-label, multi-center study comparing the safety and efficacy of efavirenz to tenofovir when administered in combination with an investigational abacavir/lamivudine (600mg/300mg daily) fixed-dose combination tablet as a once-daily regimen. Shortly after initiation of this study, GlaxoSmithKline received reports from investigators of poor efficacy in patients receiving tenofovir/lamivudine/abacavir. An unplanned interim analysis was conducted to assess virologic non-response, defined as either (a) failure to achieve a 2 log decrease from baseline by treatment week 8 or (b) a 1 log increase above nadir on any subsequent treatment visit. Accordingly, 49% of patients in the tenofovir group (compared to 5% in the efavirenz group) who had been on therapy for at least eight weeks meet the definition of virologic non-response.

The precise nature of the non-response in this study is not known. Possible explanations include an intracellular pharmacokinetic reaction of the rapid emergence of resistance. Preliminary genotypes of viral isolates from 14 patients with non-response taking the tenofovir regimen have shown all 14 isolates had the M184V mutation in HIV reverse transcriptase. In addition, 8/14 (57%) isolates also had the K65R mutation (which confers resistance to both abacavir and tenofovir).

On review of these results, GSK promptly informed all participating clinical investigators and terminated the tenofovir arm in this study. And in addition to these results, a pilot study reported by Dr. Charles Farthing at the 2nd International AIDS Society Conference on HIV Pathogenesis and Treatment provided data in 20 patients receiving tenofovir/lamivudine/abacavir once daily for initial therapy. As in ESS30009, a high rate of virologic non-response was documented (Farthing, 2003).

Similarly, on October 14, Gilead Sciences issued a "Dear Healthcare Provider" letter indicating a disastrous virologic failure rate of 91% in a 12-week pilot study evaluating once-daily tenofovir, lamivudine, and didanosine EC.

"Although zidovudine/lamivudine/abacavir appeared comparable to indinavir- or nelfinavir-based regimens in initial studies, we now know that this regimen is inferior virologically to an efavirenz-based regimen for the initial treatment of HIV infection," commented Dr. Gulick. "Other triple-nucleoside regimens are associated with unexpectedly high virologic failure rates. Taken together, these data disfavor the routine use of triple-nucleoside regimens for initial HIV therapy."

Once-Daily Regimens

THERE ARE A GROWING NUMBER OF ANTIRETROVIRALS BECOMING AVAILABLE for once-daily administration. At the present time, amprenavir/ritonavir, atazanavir (Reyataz), efavirenz, emtricitabine (Emtriva), didanosine, lamivudine, stavudine extended release (Zerit XR; not yet available in pharmacies), and tenofovir are all approved by the FDA for once-daily administration. Also under investigation are once-daily dosing schedules for abacavir, nevirapine, and a handful of ritonavir-boosted PI regimens.

Without doubt, there is a great deal of interest in complete antiretroviral regimens that only need to be taken once a day, given that they are both convenient and potentially linked to better adherence. However, one major concern with once-daily regimens is the paucity of data from long-term clinical trials comparing once-daily regimens to standard

twice-daily regimens. While a number of antiretrovirals are now approved for once-daily use, the fact of the matter is that they were typically studied in clinical trials where other components of the regimen were given twice a day.

Another lingering concern is the consequence of missed doses. The outcome of missing doses is highly dependent on the pharmacology of the active antiretroviral drug (e.g., C_{min}, elimination half-life, intracellular drug concentrations, and the IC_{50} of an individual patient's HIV isolate). The greater the C_{min}:IC_{50} ratio and the longer the half-life of the drug, the more likely it would be for the C_{min} to remain over the HIV-isolate's IC_{50} despite missing one dose. On the contrary, when an antiretroviral agent with a low C_{min}:IC_{50} ratio and a relatively short half-life is given as once-daily dosing, missing one dose may result in inadequate drug exposure over a defined period of time leading to a higher probability of development of drug resistance.

Balancing the potential benefits of once-daily therapy with its potential drawbacks, the *Guidelines* endorse once-daily regimens, but only with NRTIs that have PK profiles that justify once-daily use—which include didanosine, lamivudine, and tenofovir—plus efavirenz. Other agents with once-daily potential include nevirapine and ritonavir-boosted PIs with established once-daily efficacy, including ritonavir/amprenavir and possibly ritonavir/saquinavir. At the same time, Dr. Dybul pointed out, "the *Guidelines* specify that additional clinical trial data with longer follow-up are needed to support the routine use of these less conventional dosing strategies."

III. Initiating Changes in Antiretroviral Therapy

IN KEEPING UP WITH THE UNFORTUNATE REALITY OF TREATMENT FAILURE in HIV-positive individuals, the *Guidelines* continue to expand upon—and simplify—its criteria for changing therapy when necessary.

Heading the list of criteria for changing or modifying an antiretroviral regimen is virologic failure. Virologic failure can be divided into two categories: incomplete virologic response or virologic rebound. An incomplete virologic response, at least among HIV-positive individuals initiating therapy for the first time, is defined by the *Guidelines* as failure to achieve fewer than 400 HIV-RNA copies/mL by week 24 of treatment or fewer than 50 HIV-RNA copies/mL by week 48 of treatment. The time course of response can vary and appears to be dependent on the pretreatment viral load; it may take longer for individuals with high pretreatment viral loads (e.g., greater than 100,000 copies/mL) to achieve HIV-RNA levels below 400 and 50 copies/mL than individuals with lower pretreatment HIV-RNA titers. It's also important to recognize that the timing, pattern, and/or slope of HIV-RNA decrease may predict the ultimate virologic response. For example, most patients with an adequate virologic response (below 400 copies/mL) after 24 weeks of treatment had at least a 1 log reduction in HIV-RNA within one to four weeks after starting therapy. As for virologic rebound, the definition is much more direct: repeated detectable viremia, after virologic suppression, is indicative of virologic failure.

With respect to low-level viremia in the setting of therapy, there is no consensus regarding the best time to alter the regimen being used. The most aggressive approach would be to change for any repeated, detectable viremia (e.g., two consecutive viral load titers above 400 copies/mL after a period of undetectability). Other, less strict approaches allow detectable viremia up to an arbitrary level (e.g., 1,000 to 5,000 copies/mL). However, ongoing viral replication in the presence of antiretroviral drugs promotes the selection of drug resistance mutations. Isolated episodes of viremia—"blips" (e.g. single bursts of 50 to 1,000 copies/mL)—usually are not associated with subsequent virologic failure, but rebound to higher viral load levels or more frequent episodes of viremia increase the risk of failure.

Considering that a primary goal of therapy is to restore and preserve immune function, CD4+ cell count responses to treatment are a vital fac-

Table 3. **Summary of Guidelines for Changing an Antiretroviral Regimen For Suspected Treatment Regimen Failure**

Patient Assessment

- Review antiretroviral treatment history.
- Perform physical exam to assess for signs of clinical progression.
- Assess adherence, tolerability, and pharmacokinetic issues.
- Distinguish between first or second, and multiple treatment regimen failures.
- Perform resistance testing while patient is taking therapy (see Table 5).
- Identify susceptible drugs and drug classes.

Patient Management: Specific Clinical Scenarios

- Limited prior treatment with low (but not suppressed) HIV RNA level (e.g., up to 5000 copies/mL): The goal of treatment is to re-suppress viral replication. Consider intensifying with one drug (e.g., tenofovir) or pharmacokinetic enhancement (use of ritonavir boosting of a protease inhibitor), or most aggressively, change to a completely new regimen. If continuing the same treatment regimen, need to follow HIV RNA levels more closely, because ongoing viremia will lead to the accumulation of resistance mutations.
- Limited prior treatment with single drug resistance: Consider changing one drug, pharmacokinetic enhancement (few data available), or, most aggressively, change to a completely new regimen.
- Limited prior treatment with more than 1 drug resistance: The goal of treatment is to suppress viremia to prevent further selection of resistance mutations. Consider optimizing regimen by changing classes (e.g., PI-based to NNRTI-based and vice versa) and/or adding new active drugs. (See Table 4).
- Prior treatment with no resistance identified: Consider the timing of obtaining the drug resistance test (e.g., was the patient off antiretroviral medications?) and/or nonadherence. Consider resuming the same regimen or starting a new regimen and then repeating genotypic testing early (e.g., 2–4 weeks) to see if a resistant strain has been selected.
- Extensive prior treatment: It is reasonable to continue the same antiretroviral regimen if there are few or no treatment options. In general, avoid adding a single active drug because of the risk for the development of resistance to that drug. In advanced disease with a high likelihood of clinical progression, adding a single drug may reduce the risk of immediate clinical progression. In this complicated scenario, expert advice should be sought.

Source: Panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services (DHHS) and the Henry J. Kaiser Family Foundation. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* [Table 23]. November 10, 2003. Access at: http://www.aidsinfo.nih.gov/guidelines/adult/AA_111003.html#table23

tor to consider in gauging the success of a selected drug regimen. The *Guidelines* define immunologic failure—a primary criterion for changing therapy—as a failure to increase the CD4+ count by at least 25 to 50 cells/mm^3 over the first year of therapy or a decrease to below the pretreatment CD4+ cell count while on therapy. Mean increases in CD4+ counts, among those starting therapy for the first time, are approximately 150 cells/mm^3 over the first year. Clinicians shouldn't be surprised if they observe an initial rise in some patients' CD4+ counts, followed by a more blunted response.

Clinical failure is perhaps the most important criterion to consider in deciding whether or not a change is necessary. Occurrence or recurrence of an HIV-related event—after at least three months on an antiretroviral regimen, excluding immune reconstitution syndromes—is reason enough to change a regimen, irrespective of the CD4+ cell count or viral load.

The specific clinical scenarios that may warrant a change to a prescribed antiretroviral regimen are reviewed in Table 23 of the *Guidelines* (Table 3 in this review). The *Guidelines* also describe a number of novel strategies that have been explored for treatment-experienced patients with few available active treatment options. These are reviewed in Table 24 of the *Guidelines* (Table 4 in this review).

What to Switch To?
Boosted Protease Inhibitors in Clinical Trials

AS EXPLAINED BY DR. GULICK, A NUMBER OF LESSONS HAVE BEEN LEARNED from earlier clinical trials evaluating switches from one antiretroviral regimen to another because of virologic failure. "The best responses upon switching regimens are seen in patients with lower HIV-RNA levels at the time of switching, the possibility of using a class of drugs to which the patient's virus is still sensitive, and using a protease inhibitor boosted with ritonavir," he said. More solid data from clinical trials have emerged in recent years, most notably in studies evaluating ritonavir-boosted protease inhibitor regimens. Lopinavir/ritonavir (lopinavir/r; Kaletra), for example, has been shown to be an effective option for patients failing an initial protease-inhibitor based regimen. In one study (M97-765) reviewed by Dr. Gulick, the safety and antiviral activity of lopinavir/r were evaluated in 70 NNRTI-naive patients with HIV-RNA levels between 1,000 and 100,000 copies/mL while on a first protease inhibitor-based regimen (Benson, 2002). Patients were randomized to substitute only the protease inhibitor with lopinavir/r, 400/100 mg or 400/200 mg twice daily. On day 15, nevirapine was added, and nucleoside reverse-transcriptase inhibitors were changed. Despite a greater than fourfold reduction in phenotypic susceptibility to the previously used protease inhibitor in 63% of patients, mean HIV-RNA levels declined by 1.14 log copies/mL after two weeks of lopinavir/r. At week 48, 76% of subjects receiving treatment had HIV-RNA levels below 50 copies/mL—one of the most substantial and durable responses ever seen in patients switching from one protease inhibitor to another because of virologic failure.

Dr. Gulick also reviewed data from the MaxC$_{min}$2 study, a head-to-head comparison of two boosted protease inhibitors: lopinavir/ritonavir and saquinavir/ritonavir. Of the 339 patients enrolled into the study, approximately 32% had failed an initial protease-inhibitor based regimen prior to entering the trial. The risk of virologic failure was significantly higher in the saquinavir/ritonavir group, compared to the lopinavir/ritonavir group, in the intent-to-treat analysis (ITT/e, which included all randomized patients who took at least one dose of the assigned treatment). And after 48 weeks of treatment, 65% of patients in the lopinavir/ritonavir group—compared to 57% of patients in the saquinavir/ritonavir group—had HIV-RNA levels below 50 copies/mL in the ITT/e analysis. However, this difference was not statistically significant.

Ritonavir-boosted atazanavir (Reyataz) has also been evaluated as a contender for patients with prior protease inhibitor experience. In one study (BMSAI424-045) reported at the Second International AIDS Society Conference on HIV Pathogenesis and Treatment, held this past summer in Paris, 358 patients with a history of multiple treatment failures were randomized to receive either atazanavir (300 mg QD) plus ritonavir (100 mg QD), atazanavir (400 mg QD) plus saquinavir (Invirase) (1200 mg QD), or standard doses of lopinavir/ritonavir (Kaletra) (Badaro, 2003). All patients also received tenofovir plus one nucleoside reverse transcriptase inhibitor.

At baseline, the median viral load was 4.4 log copies/mL and the CD4+ count was approximately 300 cells/mm^3. After 24 weeks of treatment, 39% of patients in the atazanavir/ritonavir group and 42% of patients in the lopinavir/ritonavir group had HIV-RNA levels below 50 copies/mL, with no statistically significant differences between the two. Similarly, actual viral load reductions were similar in both groups (–1.86 log copies/mL in the atazanavir/ritonavir group and –1.89 in the lopinavir/ritonavir group). Patients in the atazanavir/saquinavir arm had a less impressive showing:

Table 4. **Novel Strategies To Consider For Treatment-Experienced Patients With Few Available Active Treatment Options**

- Pharmacokinetic enhancement with ritonavir may increase drug concentrations and may overcome some degree of drug resistance.
- Therapeutic Drug Monitoring may be considered (see TDM discussion in this article).
- Re-treating with prior medications may be useful, particularly if they were discontinued previously for toxicities that can now be better addressed. Continued drug pressure and drug substitutions may compromise viral replicative capacity and viral fitness, but it is not known if this has clinical applicability.
- The use of empiric multidrug regimens (including up to 3 PIs and/or 2 NNRTIs) has been advocated by some (Montaner, 2001; Youle, 2002), but may be limited ultimately by complexity, tolerability, and drug-drug interactions.
- Structured treatment interruptions in the setting of virologic failure have been investigated prospectively, but results are conflicting (Lawrence, 2003; Katlama, 2003). The risks of this approach (CD4 cell decline, HIV-related clinical events including death, acute retroviral syndrome) appear to outweigh any possible benefit (decreased HIV RNA levels on the next treatment regimen). Given the seriousness of the risks and the unproven benefits, this strategy cannot be recommended.
- New antiretroviral drugs (drugs in existing classes with activity against resistant viral strains, or new drug classes with novel mechanisms of action) including those available on expanded access or through clinical trials may be used. Enfuvirtide (T-20) recently was approved for use in the treatment-experienced patient with ongoing viremia on the basis of antiretroviral activity in this population (Lalezari, 2003; Lazzarin, 2003). Given the necessity for parenteral (subcutaneous) administration twice daily, this drug should be reserved for heavily treatment-experienced patients.

Source: Panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services (DHHS) and the Henry J. Kaiser Family Foundation. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* [Table 24]. November 10, 2003. Access at: http://www.aidsinfo.nih.gov/guidelines/adult/AA_111003.html#table24

Table 5. **Recommendations for Using Drug-Resistance Assays**

Clinical Setting/Recommendation	Rationale
Drug-resistance assay recommended	
Virologic failure during combination antiretroviral therapy	Determine the role of resistance in drug failure and maximize the number of active drugs in the new regimen, if indicated.
Suboptimal suppression of viral load after antiretroviral therapy initiation	Determine the role of resistance and maximize the number of active drugs in the new regimen, if indicated.
Acute human immunodeficiency virus (HIV) infection, if decision is made to initiate therapy	Determine if drug-resistant virus was transmitted and change regimen accordingly.
Drug-resistance assay should be considered	
Chronic HIV infection before therapy initiation	Available assays might not detect minor drug-resistant species. However, should consider if significant probability that patient was infected with drug-resistant virus (i.e., if the patient is thought to have been infected by a person receiving antiretroviral drugs).
Drug resistance assay not usually recommended	
After discontinuation of drugs	Drug-resistance mutations might become minor species in the absence of selective drug pressure, and available assays might not detect minor drug-resistant species. If testing is performed in this setting, the detection of drug resistance may be of value, but its absence does not rule out the presence of minor drug-resistant species.
Plasma viral load < 1000 HIV-RNA copies/mL	Resistance assays cannot be consistently performed because of low copy number of HIV RNA; patients/providers may incur charges and not receive results.

Source: Panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services (DHHS) and the Henry J. Kaiser Family Foundation. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* [Table 3]. November 10, 2003. Access at: http://www.aidsinfo.nih.gov/guidelines/adult/AA_111003.html#table3

only 23% had HIV-RNA levels below 50 copies/mL and the median viral load reduction was 1.52 below baseline values after 24 weeks of therapy.

IV. Drug-Resistance Testing

DRUG-RESISTANCE TESTING CONTINUES TO PROVE USEFUL FOR HIV-POSITIVE individuals experiencing virologic failure while on antiretroviral therapy. Data from retrospective and prospective clinical trials—employing genotypic resistance testing, phenotypic resistance testing, or both—have consistently demonstrated that drug-resistance testing improves short-term virologic responses to second-line, third-line, and salvage regimens, compared to responses observed when changes in therapy were guided by clinical judgment only. In turn, resistance testing is recommended in the *Guidelines* to determine the role of resistance in drug failure and to maximize the number of active drugs in the new regimen, if indicated (see Table 5).

No prospective data exist to support using one type of resistance assay over another (i.e., genotyping versus phenotyping) in different clinical situations. Therefore, one type of assay is recommended per sample; however, for patients with a complex treatment history, both assays might provide critical and complementary information.

As has been reviewed in several past issues of the *Notebook* (see "Transmission of Drug-Resistant HIV-1," a summary of a lecture delivered by Dr. Viviana Simon published in September 2003), transmission of drug-resistant HIV strains has been documented and has been associated with a suboptimal virologic response to initial antiretroviral therapy. If the decision is made to initiate therapy in a person with acute HIV infection, it is likely that resistance testing at baseline will optimize virologic response, although this strategy has not been tested in prospective clinical trials. Because of its more rapid turnaround time, using a genotyping assay might be preferred in this situation. Since some resistance-associated mutations are known to persist in the absence of drug pressure, it may be reasonable to extend this strategy for one to two years post-seroconversion.

Using resistance testing before initiation of antiretroviral therapy in patients with chronic HIV infection is less straightforward. Available resistance assays might fail to detect drug-resistant species that were transmitted when primary infection occurred but, with the passage of time, became a minor species in the absence of selective drug pressure. As with acute HIV infection, prospective evaluation of "baseline" resistance testing in this setting has not been performed. It may be reasonable to consider such testing, however, when there is a significant probability that the patient was infected with a drug-resistant virus—for example, if the patient is thought to have been infected by a person who was receiving antiretroviral drugs.

V. Therapeutic Drug Monitoring

DETERMINING THE REASONS FOR ANTIRETROVIRAL TREATMENT FAILURE has long been a frustrating question for researchers and clinicians alike. Very often, the underlying causes of therapeutic failure in individual HIV-positive patients are established after the fact—when viral load has rebounded and a switch to a second-line regimen is inevitable. But times are changing and, with new laboratory markers such as therapeutic drug monitoring (TDM), intervention before virologic failure occurs has become a possibility.

TDM is a somewhat complicated laboratory test that allows researchers and clinicians to measure blood levels of antiretroviral drugs and, as a result, adjust dosing in an individualized manner. TDM is currently recommended by the British HIV Association and the French Department of Health and is being offered by a number of laboratories

in the Netherlands, France, and England. While TDM is not typically employed in the United States, most clinicians are familiar with its usefulness, particularly for patients being treated with drugs with narrow therapeutic indices (e.g., phenytoin (Dilantin), digoxin (Lanoxin), lithium bicarbonate, and theophylline).

As reviewed in the most recent DHHS *Guidelines*, there are a number of possible scenarios in which TDM might be useful to the clinician. First, it can help to identify clinically significant drug-drug or drug-food interactions that may result in reduced efficacy or increased dose-related toxicities. Second, it may help guide dosing of antiretrovirals in the setting of specific pathophysiologic states associated with the impairment of gastrointestinal, hepatic, or renal function that can alter drug absorption, distribution, metabolism, or elimination. TDM may also be useful in monitoring HIV-positive pregnant women undergoing treatment, who may be at risk for virologic failure as a result of varying pharmacokinetics not typically seen in non-pregnant HIV-positive patients. It may also be useful in figuring out why an antiretroviral regimen is not working as well as it should in an antiretroviral-naive patient—before resistance-associated mutations develop.

Another possibility highlighted by Dr. Gulick for using TDM is to boost the inhibitory quotient (IQ) of a particular drug to overcome drug resistance. Because drug resistance is relative, increasing the drug dose—and concentrations—may overcome resistance; of course, the limiting factor with this approach in many cases is drug toxicity associated with higher doses. In a nutshell, the IQ is the ratio of a measure of drug concentration to a measure of virus susceptible to the drug. The higher the IQ, the better the buffer zone—a therapeutic pillow—between drug concentrations that are active against drug-resistant or wild-type virus and drug concentrations that allow for the emergence of drug-resistant mutants. The IQ is expressed as the actual trough (C_{min}) concentration over that of the *in vitro* IC_{50} or IC_{95} of both wild-type and mutant virus, determined by using phenotypic assays or virtual phenotypic testing (i.e., $IQ = C_{min}/IC_{95}$).

Drugs with the lowest IQ are more likely to be associated with poor virologic outcome, whereas those with high IQs are more likely to stay on top of and maintain control of viral replication. While this theory needs to be examined much more carefully and validated in prospective clinical trials, it is clear that individual protease inhibitors experience a remarkable boost in their IQ with the use of ritonavir (Norvir) as a pharmacologic enhancer. "Here is where TDM can come in," explained Dr. Gulick. "Given that protease inhibitor levels are the most amenable to manipulation, we may be able to use TDM to increase a protease inhibitor's IQ to overcome resistance measured by using phenotypic assays."

However, there are several challenges and scientific gaps to the implementation of TDM in the clinical setting. The therapeutic range is a range of concentrations established through clinical investigations that are associated with achieving the desired therapeutic response and/or reducing the frequency of drug-associated adverse reactions. Therefore, the key characteristic of a drug that is a candidate for TDM is knowledge of a therapeutic range of concentrations. Implementation of TDM in a patient requires the quantification of the concentration of the drug, usually in plasma or serum; the determination of the patient's pharmacokinetic characteristics; interpretation of the concentrations; and adjustment of the drug dose to achieve concentrations within the therapeutic range if necessary—a complex process that has not been standardized.

As knowledge of associations between antiretroviral concentrations and virologic response continues to accumulate, clinicians employing a TDM strategy for patient management should consult the most current literature. Table 26 of the *Guidelines* (Table 6 in this review) presents a synthesis of recommendations for minimum target trough PI and NNRTI concentrations in persons with wild-type virus. Unfortunately, fewer data are available to formulate suggestions for minimum target trough concentration in treatment-experienced patients who have viral isolates with reduced susceptibility to these agents. It is likely that use of these agents in the setting of reduced viral susceptibility may require higher trough concentrations than those for wild-type virus. Information on relationships between concentrations and drug-associated toxicities are also sparse, and clinicians using TDM as a strategy to manage these toxicities also should consult the most current literature for specific concentration recommendations.

Table 6. **Suggested Minimum Target Trough Concentrations for Persons with Wild-Type HIV**

Drug	Concentration (ng/mL)
Amprenavir (Agenerase)	400
Indinavir (Crixivan)	100
Lopinavir/ritonavir (Kaletra)	1000
Nelfinavir (Viracept) a	800
Ritonavir (Norvir) b	2100
Saquinavir (Fortovase, Invirase)	100–250
Efavirenz (Sustiva)	1000
Nevirapine (Viramune)	3400

a. Measurable active (M8) metabolite.

b. Ritonavir given as a single PI.

Source: Panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services (DHHS) and the Henry J. Kaiser Family Foundation. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* [Table 26]. November 10, 2003. Access at: http://www.aidsinfo.nih.gov/guidelines/adult/AA_111003.html#table26

The most striking limiting factor for the implementation of TDM at present is the lack of prospective studies demonstrating that TDM improves clinical outcome. Additional limitations are the lack of widespread availability of laboratories that perform quantitation of antiretroviral drug concentrations under rigorous quality assurance/quality control standards; the shortage of experts in the interpretation of antiretroviral concentration data; and application of such data to revise patients' dosing regimens. A final caveat to the use of measured drug concentration in patient management is a general one: Drug concentration information cannot be used alone; it must be integrated with other clinical and patient information.

Given that research into the clinical utility of TDM is still in its infancy, compounded by the fact that TDM is not widely available through commercial laboratories, the DHHS *Guidelines* do not recommend TDM for routine use in the management of HIV-infected patients.

VI. Treatment Interruptions: Can Therapy Be Stopped?

WHILE RESEARCH FOCUSING ON STRUCTURED TREATMENT INTERRUPTIONS (STIS) appears to have lost some of its steam and is rarely the late-breaking topic on the medical conference circuit, it still has not answered one of the most pressing questions haunting HIV-treating clinicians: to stop or not to stop? The reasons for wanting to halt therapy temporar-

ily are just as valid today as they once were—patients dealing with adherence issues; preventing, delaying or reversing long-term drug side effects; the potential for augmented immune responses; and the possibility of overcoming or preventing drug-resistant virus. But the data to justify STIs as safe and effective approaches remain decidedly mixed.

A Tale of Two STIs

OF PARTICULAR INTEREST TO DR. GULICK WERE DATA FROM TWO RECENT studies evaluating STIs in patients experiencing virologic failure who have few remaining treatment options to choose from. In brief, patients who initiate an STI while experiencing virologic failure on an antiretroviral drug regimen essentially remove the selective pressure being exerted on the virus. This, in theory, should permit the "optimally fit" wild-type virus to outgrow drug-resistant variants, resulting in a dominant drug-sensitive phenotypic population. And once therapy is reinitiated, a profound and perhaps durable response to therapy would ensue.

This did not appear to be the case in CPCRA 064, the results of which were recently published in *New England Journal of Medicine* by Dr. Jody Lawrence of the University of California, San Francisco, and her colleagues (Lawrence, 2003). Patients entered the study with a mean viral load of 100,000 copies/mL and had taken, on average, 11 antiretroviral drugs in the past. Before the trial was terminated because of efficacy concerns, 270 patients were randomized to take either a four-month STI or to switch to an optimized antiretroviral regimen.

Among the patients who undertook an STI, there was an initial rise in viral load of approximately 0.3 log copies/mL. After restarting therapy with an optimized regimen, the median viral load decrease was 0.75 log copies/mL below pre-STI levels. However, among those who immediately switched to an optimized regimen, there was a similar median viral load drop of 0.66 log copies/mL—with no statistically significant differences between the two groups. CD4+ counts were 7 cells/mm^3 above pre-STI levels among patients who stopped therapy for four months, compared to an increase of 42 cells/mm^3 among those who immediately switched to an optimized regimen.

More encouraging data were reported from a smaller study by Dr. Christine Katlama of the Hôpital Pitié-Salpêtrière in Paris and her colleagues (Katlama, 2003). Similar to CPCRA 064, the ANRS 097 study randomized 67 patients to do an STI or to immediately switch to another antiretroviral regimen. Unlike the CPCRA study, the ANRS study limited the STI to eight weeks and required a switch to a multiple-drug regimen consisting of eight or nine drugs (patients in CPCRA 064 typically received three- or four-drug regimens upon switching).

Among the patients who switched immediately to the multi-drug regimen, there was a total CD4+ count increase of 7 cells/mm^3 and a viral load decrease of 0.4 log copies/mL after 48 weeks. Conversely, among those in the STI group, there was a CD4+ count increase of 51 cells/mm^3 and a viral load reduction of 1.1 log copies/mL after 24 weeks. These differences were highly statistically significant.

These discrepant results have not been well explained. Whether the difference in the length of the STI—16 weeks versus eight weeks—led to the selection—or partial selection—of viral variants is not known. Certainly, the subsequent treatment regimens were different.

Based on the conflicting results of these two studies, the *Guidelines* take a conservative position on the use of STIs in the setting of virologic failure. At this time, the panelists write: "The risks of this approach (CD4+ cell decline, HIV-related clinical events including death, acute retroviral syndrome) appear to outweigh any possible benefit (decreased HIV RNA levels on the next treatment regimen). Given the seriousness of the risks and the unproven benefits, this strategy cannot be recommended." This is clearly stated in Table 24 of the *Guidelines* (Table 4 in this review).

Conclusion

WHILE BY NO MEANS A COMPREHENSIVE OVERVIEW OF THE *GUIDELINES*, Drs. Dybul's and Gulick's presentations—and by extension this article—underscore the intent of the DHHS recommendations: to promote ongoing discussion between the patient and clinician after having defined specific therapeutic goals with an acknowledgment of uncertainties. Of equal importance, the Panel on Clinical Practices for Treatment of HIV Infection remains committed to revising these guidelines as new data become available and lingering controversies are addressed, appreciating that the medical management of HIV disease is an evolving science.

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